



X-linked creatine deficiency

X-linked creatine deficiency is an inherited disorder that primarily affects the brain. People with this disorder have intellectual disability, which can range from mild to severe, and delayed speech development. Some affected individuals develop behavioral disorders such as attention deficit hyperactivity disorder or autistic behaviors that affect communication and social interaction. They may also experience seizures. Children with X-linked creatine deficiency may experience slow growth and exhibit delayed development of motor skills such as sitting and walking. Affected individuals tend to tire easily.

A small number of people with X-linked creatine deficiency have additional signs and symptoms including abnormal heart rhythms, an unusually small head (microcephaly), or distinctive facial features such as a broad forehead and a flat or sunken appearance of the middle of the face (midface hypoplasia).

Frequency

The prevalence of X-linked creatine deficiency is unknown. More than 150 affected individuals have been identified. The disorder has been estimated to account for between 1 and 2 percent of males with intellectual disability.

Genetic Changes

Mutations in the *SLC6A8* gene cause X-linked creatine deficiency. The *SLC6A8* gene provides instructions for making a protein that transports the compound creatine into cells. Creatine is needed for the body to store and use energy properly.

SLC6A8 gene mutations impair the ability of the transporter protein to bring creatine into cells, resulting in a creatine shortage (deficiency). The effects of creatine deficiency are most severe in organs and tissues that require large amounts of energy, especially the brain.

Inheritance Pattern

This condition is inherited in an X-linked pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell may or may not cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In most cases of X-linked inheritance, males experience more severe symptoms of the disorder than females. About half of females with one mutated copy of the *SLC6A8* gene in each cell have intellectual disability, learning difficulties, or behavioral problems. Other females with one mutated copy of the *SLC6A8* gene in each cell have no noticeable neurological problems.

Other Names for This Condition

- creatine transporter defect
- creatine transporter deficiency
- SLC6A8 deficiency
- SLC6A8-related creatine transporter deficiency
- X-linked creatine deficiency syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Creatine deficiency, X-linked
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1845862/>

Other Diagnosis and Management Resources

- GeneReview: Creatine Deficiency Syndromes
<https://www.ncbi.nlm.nih.gov/books/NBK3794>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Health Topic: Developmental Disabilities
<https://medlineplus.gov/developmentaldisabilities.html>
- Health Topic: Genetic Brain Disorders
<https://medlineplus.gov/geneticbraindisorders.html>
- Health Topic: Seizures
<https://medlineplus.gov/seizures.html>

Genetic and Rare Diseases Information Center

- X-linked creatine deficiency
<https://rarediseases.info.nih.gov/diseases/1608/x-linked-creatine-deficiency>

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability
https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- MalaCards: creatine transporter deficiency
http://www.malacards.org/card/creatine_transporter_deficiency
- Orphanet: X-linked creatine transporter deficiency
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=52503

Patient Support and Advocacy Resources

- Association for Creatine Deficiencies
<https://creatineinfo.org/>
- Children Living with Inherited Metabolic Diseases
<http://www.climb.org.uk/IMD/X-Ray/X-LinkedCreatineTransporterDeficiency.pdf>
- The Arc: for People with Intellectual and Developmental Disabilities
<http://www.thearc.org/page.aspx?pid=2530>

GeneReviews

- Creatine Deficiency Syndromes
<https://www.ncbi.nlm.nih.gov/books/NBK3794>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22X-linked+creatine+deficiency%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28x-linked+creatine+deficiency+syndrome%5BTIAB%5D%29+OR+%28creatine+transporter+deficiency%5BTIAB%5D%29+OR+%28creatine+transporter+defect%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- CEREBRAL CREATINE DEFICIENCY SYNDROME 1
<http://omim.org/entry/300352>

Sources for This Summary

- Braissant O, Henry H, Béard E, Uldry J. Creatine deficiency syndromes and the importance of creatine synthesis in the brain. *Amino Acids*. 2011 May;40(5):1315-24. doi: 10.1007/s00726-011-0852-z. Epub 2011 Mar 10. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21390529>
- Béard E, Braissant O. Synthesis and transport of creatine in the CNS: importance for cerebral functions. *J Neurochem*. 2010 Oct;115(2):297-313. doi: 10.1111/j.1471-4159.2010.06935.x. Epub 2010 Aug 25. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20796169>
- Clark AJ, Rosenberg EH, Almeida LS, Wood TC, Jakobs C, Stevenson RE, Schwartz CE, Salomons GS. X-linked creatine transporter (SLC6A8) mutations in about 1% of males with mental retardation of unknown etiology. *Hum Genet*. 2006 Jul;119(6):604-10. Epub 2006 Apr 26.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16738945>
- Comeaux MS, Wang J, Wang G, Kleppe S, Zhang VW, Schmitt ES, Craigen WJ, Renaud D, Sun Q, Wong LJ. Biochemical, molecular, and clinical diagnoses of patients with cerebral creatine deficiency syndromes. *Mol Genet Metab*. 2013 Jul;109(3):260-8. doi: 10.1016/j.ymgme.2013.04.006. Epub 2013 Apr 17.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23660394>
- Dunbar M, Jaggumantri S, Sargent M, Stockler-Ipsiroglu S, van Karnebeek CD. Treatment of X-linked creatine transporter (SLC6A8) deficiency: systematic review of the literature and three new cases. *Mol Genet Metab*. 2014 Aug;112(4):259-74. doi: 10.1016/j.ymgme.2014.05.011. Epub 2014 May 29. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24953403>
- Longo N, Ardon O, Vanzo R, Schwartz E, Pasquali M. Disorders of creatine transport and metabolism. *Am J Med Genet C Semin Med Genet*. 2011 Feb 15;157C(1):72-8. doi: 10.1002/ajmg.c.30292. Epub 2011 Feb 9.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21308988>
- Nasrallah F, Feki M, Kaabachi N. Creatine and creatine deficiency syndromes: biochemical and clinical aspects. *Pediatr Neurol*. 2010 Mar;42(3):163-71. doi: 10.1016/j.pediatrneurol.2009.07.015. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20159424>

- Stockler-Ipsiroglu S, van Karnebeek CD. Cerebral creatine deficiencies: a group of treatable intellectual developmental disorders. *Semin Neurol.* 2014 Jul;34(3):350-6. doi: 10.1055/s-0034-1386772. Epub 2014 Sep 5. Review. Erratum in: *Semin Neurol.* 2014 Sep;34(4):479. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25192512>
- van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S, Abulhoul L, Grünwald S, Anselm I, Azzouz H, Bratkovic D, de Brouwer A, Hamel B, Kleefstra T, Yntema H, Campistol J, Vilaseca MA, Cheillan D, D'Hooghe M, Diogo L, Garcia P, Valongo C, Fonseca M, Frints S, Wilcken B, von der Haar S, Meijers-Heijboer HE, Hofstede F, Johnson D, Kant SG, Lion-Francois L, Pitelet G, Longo N, Maat-Kievit JA, Monteiro JP, Munnich A, Muntau AC, Nassogne MC, Osaka H, Ounap K, Pinard JM, Quijano-Roy S, Poggenburg I, Poplawski N, Abdul-Rahman O, Ribes A, Arias A, Yapfite-Lee J, Schulze A, Schwartz CE, Schwenger S, Soares G, Sznajder Y, Valayannopoulos V, Van Esch H, Waltz S, Wamelink MM, Pouwels PJ, Errami A, van der Knaap MS, Jakobs C, Mancini GM, Salomons GS. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. *J Med Genet.* 2013 Jul;50(7):463-72. doi: 10.1136/jmedgenet-2013-101658. Epub 2013 May 3. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23644449>
- van de Kamp JM, Mancini GM, Salomons GS. X-linked creatine transporter deficiency: clinical aspects and pathophysiology. *J Inher Metab Dis.* 2014 Sep;37(5):715-33. doi: 10.1007/s10545-014-9713-8. Epub 2014 May 1. Review. *Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/24789340>

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